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Fish Oil (Omega-3 Fatty Acids)

Most studies indicated a benefit from Omega-3 fatty **acid** supplementation, but some researchers from the Netherlands indicated omega-3 **oil** may PROMOTE metastasis.

Evidence AGAINST **Fish Oil** Supplementation

1. 9/13/01 Diet and Cancer 1998 Quite to our surprise, we found that, in rats, **fish-oil** treatment actually promoted the development of metastatic tumors in the liver. In fact, the results were dramatic. **Fish** oils caused a 10-fold increase in the number of tumors and a 30-fold increase in their size. Plant PUFAs did not affect the number of tumors, but their size was increased by 10-fold, as compared with animals on a low-fat diet Our data also show that omega-3 PUFAs have at least two contradictory effects in relation to metastases in the liver. First, omega-3 PUFAs restrict cellular proliferation, as was shown in the first study. However, they also have the effect of inhibiting stroma formation in and around the tumors. This latter effect means that tumors can grow much faster in spite of the fact that omega-3 PUFAs inhibit cellular proliferation. We are now designing studies to investigate the effects of omega-3 PUFAs in the diets of colon-cancer patients at risk of developing liver metastases.
2. 9/13/01 Dietary omega-3 polyunsaturated fatty acids promote colon carcinoma metastasis in rat liver Cancer Res 1998 Aug 1;58(15):3312-3319 Griffini P, Fehres O, Klieverik L, Vogels IM, Tigchelaar W, Smorenburg SM, Van Noorden CJ. In conclusion, omega-3 and omega-6 PUFAs promote colon cancer metastasis in the liver without down-regulating the immune system. This finding has serious implications for the treatment of cancer patients with **fish oil** diet to fight cachexia.
3. 9/13/01 Promotion of colon cancer metastases in rat liver by **fish oil** diet is not due to reduced stroma formation. Clin Exp Metastasis 2000;18(5):371-377 Klieveri L, Fehres O, Griffini P, Van Noorden CJ, Frederiks WM. Recently, it was demonstrated that dietary omega-3 polyunsaturated fatty acids (PUFAs) induce 10-fold more metastases in number and 1000-fold in volume in an animal model of colon cancer metastasis in rat liver
4. 9/13/01 Suppression of tumor growth and metastasis by dietary **fish oil** combined with vitamins E and C and cisplatin CONCLUSIONS: Diets enriched with omega-3 PUFA may have beneficial anticancer effects in particular when containing only basal amounts of antioxidants such as vitamin E or C. Furthermore, the addition of drugs which promote oxidation of omega-3 PUFA, such as

ferrous salts (e.g. as prescribed for the treatment of anemia), may further increase these effects. However, the supportive effect of omega-3 PUFA in chemotherapy (e.g. with CP) increases when vitamins E and C are also included.

5. 9/24/01 Dr. Ornish on Omega-3 The omega-3 fatty acids have many benefits. One of the most important is that they stabilize the electrical system of your heart, thereby reducing the incidence of sudden cardiac death by 50-70%. Also, omega-3 fatty acids may reduce inflammation, lower triglycerides, and have other benefits as well. Flaxseed **oil** also is rich in the omega-3 fatty acids, but a few studies suggest that flaxseed **oil** may promote the growth of prostate cancer in men (but not breast cancer in women). Until these studies are sorted out or confirmed, I think the better part of valor would be to go with **fish oil** rather than flaxseed **oil**, at least in men.
6. 9/24/01 More Dean Ornish on Omega-3 I recommend taking small amounts of **fish oil** and flax seed **oil** -- 2 grams per day of each -- to provide the omega-3 fatty acids without taking extra omega-6 fatty acids. The only exception is for me who have prostate cancer or who are at risk for it. Dr. Charles Myers at the University of Virginia Medical School has evidence indicating that flax seed **oil** may promote the growth of prostate tumors. Someone with prostate cancer should avoid flax seed **oil** and instead take 2-3 grams per day of **fish oil**.
7. 9/13/01 Q&A with Dean Ornish - Flaxseed **Oil** may Promote Prostate Cancer The omega-3 fatty acids can be highly protective against heart disease. Flaxseed **oil** and **fish oil** are two concentrated sources of omega-3 fatty acids. However, some scientific evidence has caused me concern about recommending flaxseed **oil** because it may accelerate the progression of prostate cancer. **Fish oil**, in contrast, does not seem to have this harmful effect on prostate cancer
8. 9/24/01 Dr. Charles Myers on Omega-3
9. 9/13/01 FLAXSEED **OIL**: PROSTATE CANCER PREVENTION Men across the nation dealing with prostate cancer are passing around a spurious report that flaxseed **oil** promotes prostate cancer. Nothing could be further from the truth. The report comes from the Oct. 6 issue of the Journal of the National Cancer Institute. The primary finding of that study was that saturated fats promote prostate cancer. But an erroneous secondary finding was that omega-3 unsaturated fatty acids (alpha linolenic **acid**) were also to blame. The study in question never tested flaxseed **oil**. The report mistakenly indicates omega-3 oils in meats (not vegetables) promote prostate tumors. But meats contain very little omega-3 fatty acids. Omega6 oils such as from corn **oil** and saturated fats in dairy and meat products are the true culprits in prostate cancer.

Evidence FOR Omega-3 Supplementation

10. 9/24/01 Omega-3 Fatty Acids Description, dose recommendations from Web MD
11. 9/13/01 Omega-3 Fatty Acids Dosage, guidelines for use
12. 8/23/01 TITLE: Approaches for chronic disease prevention based on current understanding of underlying mechanisms. AUTHOR: Weisburger JH SOURCE: Am J Clin Nutr; 71(6 Suppl):1710S-4S; discussion 1715S-9S 2000 UI: 20298230 **Fish**-eating populations have lower incidences of heart disease and of many types of cancers than do other populations, which may be the result of the n-3 polyunsaturated oils found in **fish**. Among other dietary practices that may reduce the risk of cancer and cardiovascular disease are consuming 5-9 servings of fruits and

vegetables daily, which provides antioxidants such as quercetin and isothiocyanates; having a high fiber intake, including bran cereal; and drinking 1.5-2.5 L of fluids daily. Tea polyphenols found in black and green tea may have a protective effect against heart disease and some cancers

13. 9/5/01 Some Facts about Flaxseed Dr. Paul Goss, a breast cancer researcher at the University of Toronto, told attendees that brown flaxseed in a diet can have a preventive effect on breast and colon cancers. While not typically included in American diets, he said, it is a common ingredient in several parts of Europe.
14. 8/30/01 THROMBOSIS PREVENTION (LEF) In patients affected with different tumors, disorders concerning blood clotting are frequently observed. The biological processes leading to coagulation are probably involved in the mechanisms of metastasis Anticoagulant treatment of cancer patients, particularly those with lung cancer, has been reported to improve survival. These interesting, although preliminary, results of controlled trials lent some support to the argument that activation of blood coagulation plays a role in the natural history of tumor growth
15. 8/26/01 TITLE: Modulation of experimental colon tumorigenesis by types and amounts of dietary fatty acids. AUTHOR: Rao CV, Hirose Y, Indranie C, Reddy BS SOURCE: Cancer Res; 61(5):1927-33 2001 UI: 21174961 These observations demonstrate for the first time that HFML diets containing high levels of saturated fatty acids (such as those in Western diets) promote colon carcinogenesis. Although the mechanisms involved in colon tumor promotion by a HFML diet are not fully known, our results indicate that the modulation of eicosanoid production via the influence on COX activity and the suppression of apoptosis may play a key role in HFML diet-induced colon tumorigenesis.
16. 8/26/01 TITLE: n-6 and n-3 polyunsaturated fatty acids differentially modulate oncogenic Ras activation in colonocyt SOURCE: Am J Physiol Cell Physiol; 280(5):C1066-75 2001 UI: 21185313 AUTHOR: Collett ED, Davidson LA, Fan YY, Lupton JR, Chapkin RS In view of the central role of oncogenic Ras in the development of colon cancer, the finding that n-3 and n-6 PUFA differentially modulate Ras activation may partly explain why dietary **fish oil** protects against colon cancer development.
17. 8/26/01 TITLE: Pharmacological inhibition of fatty **acid** synthase activity produces both cytostatic and cytotoxic effects modulated by p53. AUTHOR: Li JN, Gorospe M, Chrest FJ, Kumaravel TS, Evans MK, Han WF, Pizer ES SOURCE: Cancer Res; 61(4):1493-9 2001 UI: 21139084 Fatty **acid** synthetic metabolism is abnormally elevated in tumor cells, and pharmacological inhibitors of the anabolic enzyme fatty **acid** synthase (FAS), including the natural product cerulenin and the novel synthetic compound c75, are selective inhibitors of tumor cell growth
18. 8/26/01 TITLE: Suppression of tumor cell growth both in nude mice and in culture by n-3 polyunsaturated fatty acids: mediation through cyclooxygenase-independent pathways SOURCE: Cancer Res; 61(4):1386-91 2001 UI: 21139067 AUTHOR: Boudreau MD, Sohn KH, Rhee SH, Lee SW, Hunt JD, Hwang DH Dietary n-3 polyunsaturated fatty acids (PUFAs), as compared with n-6 PUFAs, suppress cellular production of prostaglandins and tumor cell growth both in vitro and in vivo.
19. 8/26/01 TITLE: Biomarkers in colorectal cancer. AUTHOR: Owen RW SOURCE: IARC Sci Publ; 154:101-11 2001 UI: 21115171 High dietary levels of n-6 fatty acids appear to be important here and may also increase eicosanoid or isoprostane exposure and provide a selective growth stimulus for tumour precursor cells. Low dietary calcium may lead to inhibition of apoptosis and

possibly to an increase in cell proliferation. In three recently completed intervention trials, calcium moderately reduced the recurrence of adenomas, but in one study fibre increased recurrence dramatically.

20. 8/26/01 TITLE: Possible mechanisms relating diet and risk of colon cancer. AUTHOR: Bruce WR, Giacca A, Medline A SOURCE: Cancer Epidemiol Biomarkers Prev; 9(12):1271-9 2000 UI: 21022019 The resulting focal proliferation and mutagenesis give rise to aberrant crypt foci and adenomas. The process is inhibited by: (a) demulcents confined to the colonic lumen that "repair" the surface; (b) anti-inflammatory agents; or (c) antioxidants

21. 8/26/01 TITLE: Docosahexaenoic acid is a potent inducer of apoptosis in HT-29 colon cancer cells. SOURCE: Prostaglandins Leukot Essent Fatty Acids; 63(5):301-8 2000 UI: 20545762 AUTHOR: Chen ZY, Istfan NW In the present studies, we compared the potency of a variety of n-3 and n-6 fatty acids in modulating the apoptotic cell death in HT-29 colon cancer cells. Of all fatty acids examined, we found that docosahexaenoic acid (22:6n-3; DHA) is a potent inducer of apoptosis in a time- and dose-dependent manner

22. 8/26/01 TITLE: Dietary fish oil reduces O6-methylguanine DNA adduct levels in rat colon in part by increasing apoptosis during tumor initiation. AUTHOR: Hong MY, Lupton JR, Morris JS, Wang N, Carroll RJ, Davidson LA, Elder RH, Chapkin RS SOURCE: Cancer Epidemiol Biomarkers Prev; 9(8):819-26 2000 UI: 20406631 There is epidemiological, clinical, and experimental evidence that dietary fish oil, containing n-3 polyunsaturated fatty acids, protects against colon tumor development

23. 8/26/01 TITLE: Effect of dietary fatty acids on tumorigenesis of colon cancer induced by methyl nitrosourea in rats. AUTHOR: Zhou S, Wang G, Chen B, Wang P SOURCE: J Environ Pathol Toxicol Oncol; 19(1-2):81-6 2000 UI: 20361447 The results showed that the incidence of colon cancer and the average volume of the tumors in animals fed with diets that contained mainly beef tallow, soybean oil, or alkana oil were significantly higher than that in animals fed with diets that contained mainly fish oil

24. 8/26/01 TITLE: omega-3 fatty acids decrease endothelial adhesion of human colorectal carcinoma cells. AUTHOR: Kontogiannia M, Gupta A, Ntanios F, Graham T, Jones P, Meterissian S SOURCE: J Surg Res; 92(2):201-5 2000 UI: 20357481 Diets rich in omega-3 fatty acids have been shown to decrease both the initiation and promotion of colon carcinogenesis although their effect on hepatic metastasis formation is less well understood. Since adhesion of human colorectal carcinoma (HCRC) cells to hepatic endothelial cells is an important step in the metastatic cascade, the effect of membrane omega-3 fatty acid alterations on endothelial cell adhesion was studied.

25. 8/26/01 TITLE: Synthesis and antitumor activity of an inhibitor of fatty acid synthase. AUTHOR: Kuhajda FP, Pizer ES, Li JN, Mani NS, Frehywot GL, Townsend CA SOURCE: Proc Natl Acad Sci U S A; 97(7):3450-4 2000 UI: 20202656 Compared to normal human tissues, many common human cancers, including carcinoma of the colon, prostate, ovary, breast, and endometrium, express high levels of fatty acid synthase (FAS, EC), the primary enzyme responsible for the synthesis of fatty acids. This differential expression of FAS between normal tissues and cancer has led to the notion that FAS is a target for anticancer drug development

26. 8/26/01 TITLE: The luminal short-chain fatty acid butyrate modulates NF-kappaB activity in a human colonic epithelial cell line. AUTHOR: Inan MS, Rasoulpour RJ, Yin L, Hubbard AK, Rosenberg DW, Giardina C SOURCE: Gastroenterology; 118(4):724-34 2000 UI: 20200329

27. 8/26/01 TITLE: Lipoxygenase inhibitors as potential cancer chemopreventives. AUTHOR: Steele VE, Holmes CA, Hawk ET, Kopelovich L, Lubet RA, Crowell JA, Sigman CC, Kelloff GJ SOURCE: Cancer Epidemiol Biomarkers Prev; 8(5):467-83 1999 UI: 99277947 Mounting evidence suggests that lipoxygenase (LO)-catalyzed products have a profound influence on the development and progression of human cancers. During the past 10 years, pharmacological agents that specifically inhibit the LO-mediated signaling pathways are now commercially available to treat inflammatory diseases such as asthma, arthritis, and psoriasis. These well-characterized agents, representing two general drug effect mechanisms, are considered good candidates for clinical chemoprevention studies. One mechanism is inhibition of LO activity (5-LO and associated enzymes, or 12-LO); the second is leukotriene receptor antagonism. Although the receptor antagonists have high potential in treating asthma and other diseases where drug effects are clearly mediated by the leukotriene receptors, enzyme activity inhibitors may be better candidates for chemopreventive intervention, because inhibition of these enzymes directly reduces fatty acid metabolite production, with concomitant damping of the associated inflammatory, proliferative, and metastatic activities that contribute to carcinogenesis

28. 8/26/01 TITLE: Carcinogen and dietary lipid regulate ras expression and localization in rat colon without affecting farnesylation kinetics. AUTHOR: Davidson LA, Lupton JR, Jiang YH, Chapkin RS SOURCE: Carcinogenesis; 20(5):785-91 1999 UI: 99265363 there was a trend toward a greater incidence of mutations in tumors from corn oil fed rats (85%) compared with fish oil fed rats (58%). Our results indicate that the carcinogen-induced changes in ras expression and membrane localization are associated with the in vivo activation of the ERK pathway. In addition, suppression of tumor development by dietary n-3 polyunsaturated fatty acids may be partly due to a combined effect on colonic ras expression, membrane localization, and mutation frequency.

29. 8/26/01 TITLE: Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. SOURCE: J Exp Med; 192(8):1197-204 2000 UI: 20490853 AUTHOR: Serhan CN, Clish CB, Brannon J, Colgan SP, Chiang N, Gronert K Here, we report that inflammatory exudates from mice treated with omega-3 polyunsaturated fatty acid and aspirin (ASA) generate a novel array of bioactive lipid signals These new compounds proved to be potent inhibitors of human polymorphonuclear leukocyte transendothelial migration and infiltration in vivo (ATL analogue > 5,12,18R-triHEPE > 18R-HEPE). Acetaminophen and indomethacin also permitted 18R-HEPE and 15R-HEPE generation with recombinant COX-2 as well as omega-5 and omega-9 oxygenations of other fatty acids that act on hematologic cells. These findings establish new transcellular routes for producing arrays of bioactive lipid mediators via COX-2-nonsteroidal antiinflammatory drug-dependent oxygenations and cell-cell interactions that impact microinflammation. The generation of these and related compounds provides a novel mechanism(s) for the therapeutic benefits of omega-3 dietary supplementation, which may be important in inflammation, neoplasia, and vascular diseases.

30. 8/26/01 TITLE: Mechanism for the antitumor and anticachectic effects of n-3 fatty acids AUTHOR: Sauer LA, Dauchy RT, Blask DE SOURCE: Cancer Res; 60(18):5289-95 2000 UI: 20468875 . Here we show that the addition of alpha-linolenic acid or EPA to arterial blood inhibits tumor FA uptake, including LA, and the subsequent conversion of LA to the mitogen 13-hydroxyoctadecadienoic acid (13-HODE) in vivo and during perfusion in situ

31. 8/26/01 TITLE: Biochemical effects of a diet containing foods enriched with n-3 fatty acids. AUTHOR: Mantzioris E, Cleland LG, Gibson RA, Neumann MA, Demasi M, James MJ

SOURCE: Am J Clin Nutr; 72(1):42-8 2000 UI: 20332043 Foods that are strategically or naturally enriched in n-3 fatty acids can be used to achieve desired biochemical effects without the ingestion of supplements or a change in dietary habits. A wide range of n-3-enriched foods could be developed to support large-scale programs on the basis of the therapeutic and disease-preventive effects of n-3 fatty acids.

32. 8/26/01 TITLE: Regulation of angiogenesis by controlling VEGF receptor. AUTHOR: Murota SI, Onodera M, Morita I SOURCE: Ann N Y Acad Sci; 902:208-12; discussion 212-3 2000 UI: 20324161 The endothelial cells treated with 0.5-5 micrograms/ml eicosapentaenoic **acid** (EPA, 20:5, n-3) for 48 h displayed a dose-dependent suppression of tube formation, VEGF-induced proliferation, and activation of p42/p44 MAP kinase but not bFGF-induced ones.

33. 8/26/01 TITLE: Inhibition of translation initiation mediates the anticancer effect of the n-3 polyunsaturated fatty **acid** eicosapentaenoic **acid**. SOURCE: Cancer Res; 60(11):2919-25 2000 UI: 20306611 AUTHOR: Palakurthi SS, Fluckiger R, Aktas H, Changolkar AK, Shahsafaei A, Harneit S, Kilic E, Halperin JA Eicosapentaenoic **acid** (EPA), an n-3 polyunsaturated fatty **acid** that is abundant in the **fish**-based diets of populations that exhibit a remarkably low incidence of cancer, exerts anticancer activity in vitro and in animal models of experimental cancer

34. 7/25/01 TITLE: Newly recognized cytotoxic effect of conjugated trienoic fatty acids on cultured human tumor cells. SOURCE: Cancer Lett; 148(2):173-9 2000 UI: 20158541 AUTHOR: Igarashi M, Miyazawa T Among the conjugated fatty acids examined, conjugated linolenic **acid** and tung **oil** fatty acids exhibited the most intense cytotoxic effects on DLD-1, HepG2, A549, MCF-7 and MKN-7 cells

35. 8/26/01 TITLE: Polyunsaturated fatty acids, melatonin, and cancer prevention. SOURCE: Biochem Pharmacol; 61(12):1455-62 2001 UI: 21271761 AUTHOR: Sauer LA, Dauchy RT, Blask DE Melatonin and n3 fatty acids acted via similar or identical G(i) protein-coupled signal transduction pathways, except that melatonin receptors and putative n3 fatty **acid** receptors were used. The results link the four factors in a common mechanism and provide new insights into the roles of dietary n6 and n3 polyunsaturated fatty **acid** intake, "light at night," and melatonin in cancer prevention in humans.

36. 9/13/01 Nutrition and Cancer QUESTION: I have always heard that omega 3 fatty acids are beneficial against heart disease but recently, I heard it was also protective against breast cancer. What are omega-3-fatty acids and is it true about the anti breast cancer properties? ANSWER Recently, scientists at the University of California, Los Angeles (UCLA) put 25 women with breast cancer on a low fat diet. This diet also included 3 grams of omega-3 fatty acids per day. The results showed that the ratio of omega-3 fatty acids to other fatty acids in the fatty tissue of the women's breast increased significantly. The proportion of omega-3 fatty acids also increased in the women's buttocks but not to the same degree. This finding suggests that **fish oil** does play a distinct role in the breast. Researchers feel that it's still too early to say whether **fish oil** lowers the risk for breast cancer or if it can halt the progression of breast cancer. Experts do not recommend consuming **fish oil** capsules due to increasing fat intake, the potential of consuming toxic levels of Vitamins A and D, and environmental contaminants that often concentrate in the **fish's** liver

37. 9/13/01 BREAST CANCER: UPDATE ON A GROWING EPIDEMIC Dr. Michael Murray. After 31 months of follow-up after the initial surgery, 21 patients developed metastases of their cancer into other body tissues. Low levels of alpha-linolenic **acid** was the first determinant of metastases in these patients. In other words, when all factors were considered, low levels of alpha-linolenic

acid was found to be the most significant contributor to the spread of cancer. Since the main cause of death in breast cancer patients is the development of cancer in other tissues, the significance of this finding is of extreme importance. The results from this study suggest that supplementing the diet with flaxseed **oil** (approximately 58% alpha-linolenic **acid**) may help prevent breast cancer, tumor invasiveness, and metastasis.

38. 9/13/01 A Fish Story Cancer. Several studies during the past five years have found that people who consume a lot of omega-3 fatty acids seem to have a decreased risk of some types of common cancers - notably breast, colon and possibly prostate. Research in this area is still relatively new, and clinical trials are necessary to determine whether there is a direct link or if other factors may be involved

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